IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ashkenazi et al.
App. No.	:	09/903,925
Filed	:	July 11, 2001
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Hamud, Fozia M

Group Art Unit 1647

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner of Patents, Washington D.C. 20231 on:

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DECLARATION OF AVI ASHKENAZI, Ph.D UNDER 37 C.F.R. § 1.132

I, Avi Ashkenazi, Ph.D. declare and say as follows: -

1. I am Director and Staff Scientist at the Molecular Oncology Department of Genentech, Inc., South San Francisco, CA 94080.

2. I joined Genentech in 1988 as a postdoctoral fellow. Since then, I have investigated a variety of cellular signal transduction mechanisms, including apoptosis, and have developed technologies to modulate such mechanisms as a means of therapeutic intervention in cancer and autoimmune disease. I am currently involved in the investigation of a series of secreted proteins over-expressed in tumors, with the aim to identify useful targets for the development of therapeutic antibodies for cancer treatment.

3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

4. Gene amplification is a process in which chromosomes undergo changes to contain multiple copies of certain genes that normally exist as a single copy, and is an important factor in the pathophysiology of cancer. Amplification of certain genes (e.g., Myc or Her2/Neu)

gives cancer cells a growth or survival advantage relative to normal cells, and might also provide a mechanism of tumor cell resistance to chemotherapy or radiotherapy.

5. If gene amplification results in over-expression of the mRNA and the corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan® PCR or the fluorescence *in situ* hybridization (FISH) assays -is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy. An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

6. I understand that according to the Patent Office, absent data demonstrating that the increased copy number of a gene in certain types of cancer leads to increased expression of its product, gene amplification data are insufficient to provide substantial utility or well established utility for the gene product (the encoded polypeptide), or an antibody specifically binding the encoded polypeptide. However, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: Avi Ashkenazi
Avi Ashkenazi, Ph.D.

Date: 9/15/03

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CURRICULUM VITAE

Avi Ashkenazi

July 2003

Personal:

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Education:

1983:	B.S. in Biochemistry, with honors, Hebrew University, Israel
1986:	Ph.D. in Biochemistry, Hebrew University, Israel

Employment:

1983-1986:	Teaching assistant, undergraduate level course in Biochemistry
1985-1986:	Teaching assistant, graduate level course on Signal Transduction
1986 - 1988:	Postdoctoral fellow, Hormone Research Dept., UCSF, and Developmental Biology Dept., Genentech, Inc., with J. Ramachandran
1988 - 1989:	Postdoctoral fellow, Molecular Biology Dept., Genentech, Inc., with D. Capon
1989 - 1993:	Scientist, Molecular Biology Dept., Genentech, Inc.
1994 -1996:	Senior Scientist, Molecular Oncology Dept., Genentech, Inc.
1996-1997:	Senior Scientist and Interim director, Molecular Oncology Dept., Genentech, Inc.
1997-1990:	Senior Scientist and preclinical project team leader, Genentech, Inc.
1999 -2002:	Staff Scientist in Molecular Oncology, Genentech, Inc.
2002-present:	Staff Scientist and Director in Molecular Oncology, Genentech, Inc.

Awards:

1988:	First prize, The Boehringer Ingelheim Award

Editorial:

Editorial Board Member: Current Biology

Associate Editor, Clinical Cancer Research.

Associate Editor, Cancer Biology and Therapy.

Refereed papers:

1. Gertler, A., Ashkenazi, A., and Madar, Z. Binding sites for human growth hormone and ovine and bovine prolactins in the mammary gland and liver of the lactating cow. *Mol. Cell. Endocrinol.* **34**, 51-57 (1984).
2. Gertler, A., Shamay, A., Cohen, N., Ashkenazi, A., Friesen, H., Levanon, A., Gorecki, M., Aviv, H., Hadari, D., and Vogel, T. Inhibition of lactogenic activities of ovine prolactin and human growth hormone (hGH) by a novel form of a modified recombinant hGH. *Endocrinology* **118**, 720-726 (1986).
3. Ashkenazi, A., Madar, Z., and Gertler, A. Partial purification and characterization of bovine mammary gland prolactin receptor. *Mol. Cell. Endocrinol.* **50**, 79-87 (1987).
4. Ashkenazi, A., Pines, M., and Gertler, A. Down-regulation of lactogenic hormone receptors in Nb2 lymphoma cells by cholera toxin. *Biochemistry Internatl.* **14**, 1065-1072 (1987).
5. Ashkenazi, A., Cohen, R., and Gertler, A. Characterization of lactogen receptors in lactogenic hormone-dependent and independent Nb2 lymphoma cell lines. *FEBS Lett.* **210**, 51-55 (1987).
6. Ashkenazi, A., Vogel, T., Barash, I., Hadari, D., Levanon, A., Gorecki, M., and Gertler, A. Comparative study on in vitro and in vivo modulation of lactogenic and somatotropic receptors by native human growth hormone and its modified recombinant analog. *Endocrinology* **121**, 414-419 (1987).
7. Peralta, E., Winslow, J., Peterson, G., Smith, D., Ashkenazi, A., Ramachandran, J., Schimerlik, M., and Capon, D. Primary structure and biochemical properties of an M2 muscarinic receptor. *Science* **236**, 600-605 (1987).
8. Peralta, E. Ashkenazi, A., Winslow, J., Smith, D., Ramachandran, J., and Capon, D. J. Distincnt primary structures, ligand-binding properties and tissue-specific expression of four human muscarinic acetylcholine receptors. *EMBO J.* **6**, 3923-3929 (1987).
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10. Pines, M., Ashkenazi, A., Cohen-Chapnik, N., Binder, L., and Gertler, A. Inhibition of the proliferation of Nb2 lymphoma cells by femtomolar concentrations of cholera toxin and partial reversal of the effect by 12-o-tetradecanoyl-phorbol-13-acetate. *J. Cell. Biochem.* **37**, 119-129 (1988).

11. Peralta, E. Ashkenazi, A., Winslow, J. Ramachandran, J., and Capon, D. Differential regulation of PI hydrolysis and adenylyl cyclase by muscarinic receptor subtypes. *Nature* **334**, 434-437 (1988).

12. Ashkenazi., A. Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functionally distinct G proteins couple different receptors to PI hydrolysis in the same cell. *Cell* **56**, 487-493 (1989).

13. Ashkenazi, A., Ramachandran, J., and Capon, D. Acetylcholine analogue stimulates DNA synthesis in brain-derived cells via specific muscarinic acetylcholine receptor subtypes. *Nature* **340**, 146-150 (1989).

14. Lammare, D., Ashkenazi, A., Fleury, S., Smith, D., Sekaly, R., and Capon, D. The MHC-binding and gp120-binding domains of CD4 are distinct and separable. *Science* **245**, 743-745 (1989).

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18. Ashkenazi, A., Marsters, S., Capon, D., Chamow, S., Figari., I., Pennica, D., Goeddel., D., Palladino, M., and Smith, D. Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin. *Proc. Natl. Acad. Sci. USA.* **88**, 10535-10539 (1991).

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27. Chamow, S., Zhang, D., Tan, X., Mhtre, S., Marsters, S., Peers, D., Byrn, R., Ashkenazi, A., and Yunghans, R. A humanized bispecific immunoadhesin-antibody that retargets CD3+ effectors to kill HIV-1-infected cells. *J. Immunol.* **153**, 4268-4280 (1994).

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53. Roth, W., Isenmann, S., Naumann, U., Kugler, S., Bahr, M., Dichgans, J., Ashkenazi, A., and Weller, M. Eradication of intracranial human malignant glioma xenografts by Apo2L/TRAIL. *Biochem. Biophys. Res. Commun.* **265**, 479-483 (1999).

54. Hymowitz, S.G., Christinger, H.W., Fuh, G., Ultsch, M., O'Connell, M., Kelley, R.F., Ashkenazi, A. and de Vos, A.M. Triggering Cell Death: The Crystal Structure of Apo2L/TRAIL in a Complex with Death Receptor 5. *Molec. Cell* **4**, 563–571 (1999).

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60. Kischkel, F.C., and Ashkenazi, A. Combining enhanced metabolic labeling with immunoblotting to detect interactions of endogenous cellular proteins. *Biotechniques* **29**, 506-512 (2000).

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Review articles:

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4. Ashkenazi, A., Capon, and D. Ward, R. Immunoadhesins. *Int. Rev. Immunol.* **10**, 217-225 (1993).
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Book:

Antibody Fusion Proteins (Chamow, S., and Ashkenazi, A., eds., John Wiley and Sons Inc.) (1999).

Talks:

1. Resistance of primary HIV isolates to CD4 is independent of CD4-gp120 binding affinity. UCSD Symposium, HIV Disease: Pathogenesis and Therapy. Greenelefe, FL, March 1991.
2. Use of immuno-hybrids to extend the half-life of receptors. IBC conference on Biopharmaceutical Halflife Extension. New Orleans, LA, June 1992.
3. Results with TNF receptor Immunoadhesins for the Treatment of Sepsis. IBC conference on Endotoxemia and Sepsis. Philadelphia, PA, June 1992.
4. Immunoadhesins: an alternative to human antibodies. IBC conference on Antibody Engineering. San Diego, CA, December 1993.
5. Tumor necrosis factor receptor: a potential therapeutic for human septic shock. American Society for Microbiology Meeting, Atlanta, GA, May 1993.
6. Protective efficiacy of TNF receptor immunoadhesin vs anti-TNF monoclonal antibody in a rat model for endotoxic shock. 5th International Congress on TNF. Asilomar, CA, May 1994.
7. Interferon-γ signals via a multisubunit receptor complex that contains two types of polypeptide chain. American Association of Immunologists Conference. San Franciso, CA, July 1995.
8. Immunoadhesins: Principles and Applications. Gordon Research Conference on Drug Delivery in Biology and Medicine. Ventura, CA, February 1996.

9. Apo-2 Ligand, a new member of the TNF family that induces apoptosis in tumor cells. Cambridge Symposium on TNF and Related Cytokines in Treatment of Cancer. Hilton-Head, NC, March 1996.
10. Induction of apoptosis by Apo2 Ligand. American Society for Biochemistry and Molecular Biology, Symposium on Growth Factors and Cytokine Receptors. New Orleans, LA, June, 1996.
11. Apo2 ligand, an extracellular trigger of apoptosis. 2nd Clontech Symposium, Palo Alto, CA, October 1996.
12. Regulation of apoptosis by members of the TNF ligand and receptor families. Stanford University School of Medicine, Palo Alto, CA, December 1996.
13. Apo-3: anovel receptor that regulates cell death and inflammation. 4th International Congress on Immune Consequences of Trauma, Shock, and Sepsis. Munich, Germany, March 1997.
14. New members of the TNF ligand and receptor families that regulate apoptosis, inflammation, and immunity. UCLA School of Medicine, LA, CA, March 1997.
15. Immunoadhesins: an alternative to monoclonal antibodies. 5th World Conference on Bispecific Antibodies. Volendam, Holland, June 1997.
16. Control of Apo2L signaling. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. Cold Spring Harbor, New York. September, 1997.
17. Chairman and speaker, Apoptosis Signaling session. IBC's 4th Annual Conference on Apoptosis. San Diego, CA., October 1997.
18. Control of Apo2L signaling by death and decoy receptors. American Association for the Advancement of Science. Philladelphia, PA, February 1998.
19. Apo2 ligand and its receptors. American Society of Immunologists. San Francisco, CA, April 1998.
20. Death receptors and ligands. 7th International TNF Congress. Cape Cod, MA, May 1998.
21. Apo2L as a potential therapeutic for cancer. UCLA School of Medicine. LA, CA, June 1998.
22. Apo2L as a potential therapeutic for cancer. Gordon Research Conference on Cancer Chemotherapy. New London, NH, July 1998.
23. Control of apoptosis by Apo2L. Endocrine Society Conference, Stevenson, WA, August 1998.
24. Control of apoptosis by Apo2L. International Cytokine Society Conference, Jerusalem, Israel, October 1998.

25. Apoptosis control by death and decoy receptors. American Association for Cancer Research Conference, Whistler, BC, Canada, March 1999.
26. Apoptosis control by death and decoy receptors. American Society for Biochemistry and Molecular Biology Conference, San Francisco, CA, May 1999.
27. Apoptosis control by death and decoy receptors. Gordon Research Conference on Apoptosis, New London, NH, June 1999.
28. Apoptosis control by death and decoy receptors. Arthritis Foundation Research Conference, Alexandria GA, Aug 1999.
29. Safety and anti-tumor activity of recombinant soluble Apo2L/TRAIL. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. . Cold Spring Harbor, NY, September 1999.
30. The Apo2L/TRAIL system: therapeutic potential. American Association for Cancer Research, Lake Tahoe, NV, Feb 2000.
31. Apoptosis and cancer therapy. Stanford University School of Medicine, Stanford, CA, Mar 2000.
32. Apoptosis and cancer therapy. University of Pennsylvania School of Medicine, Philladelphia, PA, Apr 2000.
33. Apoptosis signaling by Apo2L/TRAIL. International Congress on TNF. Trondheim, Norway, May 2000.
34. The Apo2L/TRAIL system: therapeutic potential. Cap-CURE summit meeting. Santa Monica, CA, June 2000.
35. The Apo2L/TRAIL system: therapeutic potential. MD Anderson Cancer Center. Houston, TX, June 2000.
36. Apoptosis signaling by Apo2L/TRAIL. The Protein Society, 14th Symposium. San Diego, CA, August 2000.
37. Anti-tumor activity of Apo2L/TRAIL. AAPS annual meeting. Indianapolis, IN Aug 2000.
38. Apoptosis signaling and anti-cancer potential of Apo2L/TRAIL. Cancer Research Institute, UC San Francisco, CA, September 2000.
39. Apoptosis signaling by Apo2L/TRAIL. Kenote address, TNF family Minisymposium, NIH. Bethesda, MD, September 2000.
40. Death receptors: signaling and modulation. Keystone symposium on the Molecular basis of cancer. Taos, NM, Jan 2001.
41. Preclinical studies of Apo2L/TRAIL in cancer. Symposium on Targeted therapies in the treatment of lung cancer. Aspen, CO, Jan 2001.

42. Apoptosis signaling by Apo2L/TRAIL. Wiezmann Institute of Science, Rehovot, Israel, March 2001.
43. Apo2L/TRAIL: Apoptosis signaling and potential for cancer therapy. Weizmann Institute of Science, Rehovot, Israel, March 2001.
44. Targeting death receptors in cancer with Apo2L/TRAIL. Cell Death and Disease conference, North Falmouth, MA, Jun 2001.
45. Targeting death receptors in cancer with Apo2L/TRAIL. Biotechnology Organization conference, San Diego, CA, Jun 2001.
46. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Gordon Research Conference on Apoptosis, Oxford, UK, July 2001.
47. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Cleveland Clinic Foundation, Cleveland, OH, Oct 2001.
48. Apoptosis signaling by death receptors: overview. International Society for Interferon and Cytokine Research conference, Cleveland, OH, Oct 2001.
49. Apoptosis signaling by death receptors. American Society of Nephrology Conference. San Francisco, CA, Oct 2001.
50. Targeting death receptors in cancer. Apoptosis: commercial opportunities. San Diego, CA, Apr 2002.
51. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Kimmel Cancer Research Center, Johns Hopkins University, Baltimore MD. May 2002.
52. Apoptosis control by Apo2L/TRAIL. (Keynote Address) University of Alabama Cancer Center Retreat, Birmingham, Ab. October 2002.
53. Apoptosis signaling by Apo2L/TRAIL. (Session co-chair) TNF international conference. San Diego, CA. October 2002.
54. Apoptosis signaling by Apo2L/TRAIL. Swiss Institute for Cancer Research (ISREC). Lausanne, Swizerland. Jan 2003.
55. Apoptosis induction with Apo2L/TRAIL. Conference on New Targets and Innovative Strategies in Cancer Treatment. Monte Carlo. February 2003.
56. Apoptosis signaling by Apo2L/TRAIL. Hermelin Brain Tumor Center Symposium on Apoptosis. Detroit, MI. April 2003.
57. Targeting apoptosis through death receptors. Sixth Annual Conference on Targeted Therapies in the Treatment of Breast Cancer. Kona, Hawaii. July 2003.
58. Targeting apoptosis through death receptors. Second International Conference on Targeted Cancer Therapy. Washington, DC. Aug 2003.

Issued Patents:

1. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,329,028 (Jul 12, 1994).
2. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,605,791 (Feb 25, 1997).
3. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,889,155 (Jul 27, 1999).
4. Ashkenazi, A., APO-2 Ligand. US patent 6,030,945 (Feb 29, 2000).
5. Ashkenazi, A., Chuntharapai, A., Kim, J., APO-2 ligand antibodies. US patent 6, 046, 048 (Apr 4, 2000).
6. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 6,124,435 (Sep 26, 2000).
7. Ashkenazi, A., Chuntharapai, A., Kim, J., Method for making monoclonal and cross-reactive antibodies. US patent 6,252,050 (Jun 26, 2001).
8. Ashkenazi, A. APO-2 Receptor. US patent 6,342,369 (Jan 29, 2002).
9. Ashkenazi, A. Fong, S., Goddard, A., Gurney, A., Napier, M., Tumas, D., Wood, W. A-33 polypeptides. US patent 6,410,708 (Jun 25, 2002).
10. Ashkenazi, A. APO-3 Receptor. US patent 6,462,176 B1 (Oct 8, 2002).
11. Ashkenazi, A. APO-2LI and APO-3 polypeptide antibodies. US patent 6,469,144 B1 (Oct 22, 2002).
12. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 6,582,928B1 (Jun 24, 2003).

DECLARATION OF PAUL POLAKIS, Ph.D.

I, Paul Polakis, Ph.D., declare and say as follows:

1. I was awarded a Ph.D. by the Department of Biochemistry of the Michigan State University in 1984. My scientific Curriculum Vitae is attached to and forms part of this Declaration (Exhibit A).

2. I am currently employed by Genentech, Inc. where my job title is Staff Scientist. Since joining Genentech in 1999, one of my primary responsibilities has been leading Genentech's Tumor Antigen Project, which is a large research project with a primary focus on identifying tumor cell markers that find use as targets for both the diagnosis and treatment of cancer in humans.

3. As part of the Tumor Antigen Project, my laboratory has been analyzing differential expression of various genes in tumor cells relative to normal cells. The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. We call such differentially expressed proteins "tumor antigen proteins". When such a tumor antigen protein is identified, one can produce an antibody that recognizes and binds to that protein. Such an antibody finds use in the diagnosis of human cancer and may ultimately serve as an effective therapeutic in the treatment of human cancer.

4. In the course of the research conducted by Genentech's Tumor Antigen Project, we have employed a variety of scientific techniques for detecting and studying differential gene expression in human tumor cells relative to normal cells, at genomic DNA, mRNA and protein levels. An important example of one such technique is the well known and widely used technique of microarray analysis which has proven to be extremely useful for the identification of mRNA molecules that are differentially expressed in one tissue or cell type relative to another. In the course of our research using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.

5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein

expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.

6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 5/07/04

By: Paul Polakis

Paul Polakis, Ph.D.

SV 2031808 v1

CURRICULUM VITAE

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EDUCATION:

Ph.D., Biochemistry, Department of Biochemistry,
Michigan State University (1984)

B.S., Biology. College of Natural Science, Michigan State University (1977)

PROFESSIONAL EXPERIENCE:

2002-present	Staff Scientist, Genentech, Inc S. San Francisco, CA
1999- 2002	Senior Scientist, Genentech, Inc., S. San Francisco, CA
1997 -1999	Research Director Onyx Pharmaceuticals, Richmond, CA
1992- 1996	Senior Scientist, Project Leader, Onyx Pharmaceuticals, Richmond, CA
1991-1992	Senior Scientist, Chiron Corporation, Emeryville, CA.
1989-1991	Scientist, Cetus Corporation, Emeryville CA.
1987-1989	Postdoctoral Research Associate, Genentech, Inc., South SanFrancisco, CA.
1985-1987	Postdoctoral Research Associate, Department of Medicine, Duke University Medical Center, Durham, NC

1984-1985	Assistant Professor, Department of Chemistry, Oberlin College, Oberlin, Ohio
1980-1984	Graduate Research Assistant, Department of Biochemistry, Michigan State University East Lansing, Michigan

PUBLICATIONS:

1. **Polakis, P G.** and Wilson, J. E. 1982 Purification of a Highly Bindable Rat Brain Hexokinase by High Performance Liquid Chromatography. **Biochem. Biophys. Res. Commun**. 107, 937-943.

2. **Polakis, P.G.** and Wilson, J. E. 1984 Proteolytic Dissection of Rat Brain Hexokinase: Determination of the Cleavage Pattern during Limited Digestion with Trypsin. **Arch. Biochem. Biophys**. 234, 341-352.

3. **Polakis, P. G.** and Wilson, J. E. 1985 An Intact Hydrophobic N-Terminal Sequence is Required for the Binding Rat Brain Hexokinase to Mitochondria. **Arch. Biochem. Biophys**. 236, 328-337.

4. Uhing, R.J., **Polakis,P.G.** and Snyderman, R. 1987 Isolaton of GTP-binding Proteins from Myeloid HL60 Cells. **J. Biol. Chem**. 262, 15575-15579.

5. **Polakis, P.G.**, Uhing, R.J. and Snyderman, R. 1988 The Formylpeptide Chemoattractant Receptor Copurifies with a GTP-binding Protein Containing a Distinct 40 kDa Pertussis Toxin Substrate. **J. Biol. Chem**. 263, 4969-4979.

6. Uhing, R. J., Dillon, S., **Polakis, P. G.**, Truett, A. P. and Snyderman, R. 1988 Chemoattractant Receptors and Signal Transduction Processes in Cellular and Molecular Aspects of Inflammation (Poste, G. and Crooke, S. T. eds.) pp 335-379.

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8. **Polakis, P. G.**, Snyderman, R. and Evans, T. 1989 Characterization of G25K, a GTP-binding Protein Containing a Novel Putative Nucleotide Binding Domain. **Biochem. Biophys. Res. Comun.** 160, 25-32.

9. **Polakis, P.**, Weber,R.F., Nevins,B., Didsbury, J. Evans,T. and Snyderman, R. 1989 Identification of the ral and rac1 Gene Products, Low Molecular Mass GTP-binding Proteins from Human Platelets. **J. Biol. Chem**. 264, 16383-16389.

10. Snyderman, R., Perianin, A., Evans, T., **Polakis, P.** and Didsbury, J. 1989 G Proteins and Neutrophil Function. In ADP-Ribosylating Toxins and G Proteins: Insights into Signal Transduction. (J. Moss and M. Vaughn, eds.) Amer. Soc. Microbiol. pp. 295-323.

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19. Martin, G., Yatani, A., Clark, R., **Polakis, P.**, Brown, A. M. and McCormick, F. 1992 GAP Domains Responsible for $p21^{ras}$-dependent Inhibition of Muscarinic Atrial K^+ Channel Currents. **Science** 255, 192-194.

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24. Polakis, P., Rubinfeld, B. and McCormick, F. 1992 Phosphorylation of rap1GAP in vivo and by cAMP-dependent Kinase and the Cell Cycle $p34^{cdc2}$ Kinase in vitro. **J. Biol. Chem**. 267, 10780-10785.

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61 **Polakis P**, Hart M and Rubinfeld B. 1999 Defects in the regulation of beta-catenin
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EXAMPLE 158: Detection of PRO Polypeptides That Affect Glucose or FFA Uptake by Primary Rat Adipocytes (Assay 94)

This assay is designed to determine whether PRO polypeptides show the ability to affect glucose or FFA uptake by adipocyte cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes or hyper- or hypo-insulinemia.

In a 96 well format, PRO polypeptides to be assayed are added to primary rat adipocytes, and allowed to incubate overnight. Samples are taken at 4 and 16 hours and assayed for glycerol, glucose and FFA uptake. After the 16 hour incubation, insulin is added to the media and allowed to incubate for 4 hours. At this time, a sample is taken and glycerol, glucose and FFA uptake is measured. Media containing insulin without the PRO polypeptide is used as a positive reference control. As the PRO polypeptide being tested may either stimulate or inhibit glucose and FFA uptake, results are scored as positive in the assay if greater than 1.5 times or less than 0.5 times the insulin control.

The following PRO polypeptides tested positive as stimulators of glucose and/or FFA uptake in this assay: PRO1114, PRO1007, PRO1066, PRO848, PRO1182, PRO1198, PRO1192, PRO1271, PRO1375 and PRO1387.

The following PRO polypeptides tested positive as inhibitors of glucose and/or FFA uptake in this assay: PRO1184, PRO1360, PRO1309, PRO1154, PRO1181, PRO1186, PRO1160 and PRO1384.

EXAMPLE 159: Chondrocyte Re-differentiation Assay (Assay 110)

This assay shows that certain polypeptides of the invention act to induce redifferentiation of chondrocytes, therefore, are expected to be useful for the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis. The assay is performed as follows. Porcine chondrocytes are isolated by overnight collagenase digestion of articulary cartilage of metacarpophalangeal joints of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm^2 in Ham F-12 containing 10% FBS and 4 μg/ml gentamycin. The culture media is changed every third day and the cells are then seeded in 96 well plates at 5,000 cells/well in 100μl of the same media without serum and 100 μl of the test PRO polypeptide, 5 nM staurosporin (positive control) or medium alone (negative control) is added to give a final volume of 200 μl/well. After 5 days of incubation at 37°C, a picture of each well is taken and the differentiation state of the chondrocytes is determined. A positive result in the assay occurs when the redifferentiation of the chondrocytes is determined to be more similar to the positive control than the negative control.

The following polypeptide tested positive in this assay: PRO1282, PRO1310, PRO619, PRO943, PRO820, PRO1080, PRO1016, PRO1007, PRO1056, PRO791, PRO1111, PRO1184, PRO1360, PRO1309, PRO1107, PRO1132, PRO1131, PRO848, PRO1181, PRO1186, PRO1159, PRO1312, PRO1192 and PRO1384.

It has been reported that gene amplification of a proto-oncogene is an event typically involved in the more malignant forms of cancer, and could act as a predictor of clinical outcome (Schwab *et al.*, Genes Chromosomes Cancer, 1:181-193 [1990]; Alitalo *et al.*, *supra*). Thus, *erb*B2 overexpression is commonly regarded as a predictor of a poor prognosis, especially in patients with primary disease that involves axillary lymph nodes (Slamon *et al.*, [1987] and [1989], *supra*; Ravdin and Chamness, Gene, 159:19-27 [1995]; and Hynes and Stern, Biochim Biophys Acta, 1198:165-184 [1994]), and has been linked to sensitivity and/or resistance to hormone therapy and chemotherapeutic regimens, including CMF (cyclophosphamide, methotrexate, and fluoruracil) and anthracyclines (Baselga *et al.*, Oncology, 11 (3 Suppl l):43-48 [1997]). However, despite the association of *erb*B2 overexpression with poor prognosis, the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients (*Ibid*). A recombinant humanized anti-ErbB2 (anti-HER2) monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or Herceptin™) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anticancer therapy. (Baselga *et al.*, J. Clin. Oncol., 14:737-744 [1996]).

In light of the above, there is obvious interest in identifying novel methods and compositions which are useful for diagnosing and treating tumors which are associated with gene amplification.

Summary of the Invention

The present invention concerns compositions and methods for the diagnosis and treatment of neoplastic cell growth and proliferation in mammals, including humans. The present invention is based on the identification of genes that are amplified in the genome of tumor cells. Such gene amplification is expected to be associated with the overexpression of the gene product and contribute to tumorigenesis. Accordingly, the proteins encoded by the amplified genes are believed to be useful targets for the diagnosis and/or treatment (including prevention) of certain cancers, and may act as predictors of the prognosis of tumor treatment.

In one embodiment, the present invention concerns an isolated antibody which binds to a polypeptide designated herein as PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. Often, the cell that expresses the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198. In one aspect, the isolated antibody specifically binds to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. In another aspect, the antibody induces the death of a cell which expresses a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. Often, the cell that expresses the PRO212, PRO290, PRO341, PRO535, PRO619,

PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is a tumor cell that overexpresses the polypeptide as compared to a normal cell of the same type. In yet another aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In yet another aspect, the antibody is an antibody fragment, a single-chain antibody, or an anti-idiotypic antibody which binds, preferably specifically, to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide.

In another embodiment, the invention concerns a composition of matter which comprises an antibody which binds, preferably specifically, to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition of matter comprises a therapeutically effective amount of the antibody. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In a further embodiment, the invention concerns an isolated nucleic acid molecule which encodes an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, and vectors and recombinant host cells comprising such nucleic acid molecules.

In a still further embodiment, the invention concerns a method for producing an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, wherein the method comprises culturing a host cell transformed with a nucleic acid molecule which encodes the antibody under conditions sufficient to allow expression of the antibody, and recovering the antibody from the cell culture.

The invention further concerns antagonists of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide that inhibit one or more of the functions or activities of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. Agonists of a PRO212, PRO290,

PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide are also contemplated herein.

In a further embodiment, the invention concerns an isolated nucleic acid molecule that hybridizes to the complement of a nucleic acid molecule encoding a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. The isolated nucleic acid molecule is preferably DNA, and hybridization preferably occurs under stringent hybridization and wash conditions. Such nucleic acid molecules can act as antisense molecules of the amplified genes identified herein, which, in turn, can find use in the modulation of the respective amplified genes, or as antisense primers in amplification réactions. Furthermore, such sequences can be used as part of a ribozyme and/or a triple helix sequence which, in turn, may be used in regulation of the amplified genes.

In another embodiment, the invention provides a method for determining the presence of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in a sample suspected of containing a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide, wherein the method comprises exposing the sample to an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and determining binding of the antibody to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in the sample. In another embodiment, the invention provides a method for determining the presence of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in a cell, wherein the method comprises exposing the cell to an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and determining binding of the antibody to the cell.

In yet another embodiment, the present invention concerns a method of diagnosing tumor in a mammal, comprising detecting the level of expression of a gene encoding a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher expression level in the test sample as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test tissue cells were obtained.

In another embodiment, the present invention concerns a method of diagnosing tumor in a mammal, comprising (a) contacting an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in said mammal. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence of tumor in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art.

The test sample is usually obtained from an individual suspected to have neoplastic cell growth or proliferation (*e.g.* cancerous cells).

In another embodiment, the present invention concerns a cancer diagnostic kit comprising an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and a carrier (*e.g.*, a buffer) in suitable packaging. The kit preferably contains instructions for using the antibody to detect the presence of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184,

PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in a sample suspected of containing the same.

In yet another embodiment, the invention concerns a method for inhibiting the growth of tumor cells comprising exposing tumor cells which express a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide to an effective amount of an agent which inhibits an activity and/or the expression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide, wherein growth of the tumor cells is thereby inhibited. The agent preferably is an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, a small organic and inorganic molecule, peptide, phosphopeptide, antisense or ribozyme molecule, or a triple helix molecule. In a specific aspect, the agent, *e.g.*, the anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, induces cell death. In a further aspect, the tumor cells are further exposed to radiation treatment and/or a cytotoxic or chemotherapeutic agent.

In a further embodiment, the invention concerns an article of manufacture, comprising:

a container;

a label on the container; and

a composition comprising an active agent contained within the container; wherein the composition is effective for inhibiting the growth of tumor cells and the label on the container indicates that the composition can be used for treating conditions characterized by overexpression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide as compared to a normal cell of the same tissue type. In particular aspects, the active agent in the composition is an agent which inhibits an activity and/or the expression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. In preferred aspects, the active agent is an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-

PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody or an antisense oligonucleotide.

The invention also provides a method for identifying a compound that inhibits an activity of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide, comprising contacting a candidate compound with a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide under conditions and for a time sufficient to allow these two components to interact and determining whether an activity of the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of (a) contacting cells and a candidate compound to be screened in the presence of PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide and (b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in cells that express the polypeptide, wherein the method comprises contacting the cells with a candidate compound and determining whether the expression of the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is inhibited. In a preferred aspect, this method comprises the steps of (a) contacting cells and a candidate compound to be screened under conditions suitable for allowing expression of the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005,

PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide and (b) determining the inhibition of expression of said polypeptide.

Brief Description of the Figures

Figure 1 shows the nucleotide sequence (SEQ ID NO:1) of a cDNA containing a nucleotide sequence encoding native sequence PRO212, wherein the nucleotide sequence (SEQ ID NO:1) is a clone designated herein as DNA30942-1134. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 2 shows the amino acid sequence (SEQ ID NO:2) of a native sequence PRO212 polypeptide as derived from the coding sequence of SEQ ID NO:1.

Figures 3A through 3B show the nucleotide sequence (SEQ ID NO:6) of a cDNA containing a nucleotide sequence encoding native sequence PRO290, wherein the nucleotide sequence (SEQ ID NO:6) is a clone designated herein as DNA35680-1212. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 4 shows the amino acid sequence (SEQ ID NO:7) of a native sequence PRO290 polypeptide as derived from the coding sequence of SEQ ID NO:6.

Figure 5 shows the nucleotide sequence (SEQ ID NO:9) of a cDNA containing a nucleotide sequence encoding native sequence PRO341, wherein the nucleotide sequence (SEQ ID NO:9) is a clone designated herein as DNA26288-1239. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 6 shows the amino acid sequence (SEQ ID NO:10) of a native sequence PRO341 polypeptide as derived from the coding sequence of SEQ ID NO:9.

Figure 7 shows the nucleotide sequence (SEQ ID NO:13) of a cDNA containing a nucleotide sequence encoding native sequence PRO535, wherein the nucleotide sequence (SEQ ID NO:13) is a clone designated herein as DNA49143-1429. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 8 shows the amino acid sequence (SEQ ID NO:14) of a native sequence PRO535 polypeptide as derived from the coding sequence of SEQ ID NO:13.

Figure 9 shows the nucleotide sequence (SEQ ID NO:15) of a cDNA containing a nucleotide sequence encoding native sequence PRO619, wherein the nucleotide sequence (SEQ ID NO:15) is a clone designated herein as DNA49821-1562. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 10 shows the amino acid sequence (SEQ ID NO:16) of a native sequence PRO619 polypeptide as derived from the coding sequence of SEQ ID NO:15.

Figure 11 shows the nucleotide sequence (SEQ ID NO:17) of a cDNA containing a nucleotide sequence encoding native sequence PRO717, wherein the nucleotide sequence (SEQ ID NO:17) is a clone designated herein as DNA50988-1326. Also presented in bold font and underlined are the positions of the respective start and stop

Gene amplification assay:

The PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 compounds of the invention were screened in the following primary tumors and the resulting ΔCt values are reported in Tables 3A-3D.